Self-renewal and senescence in iPS cells derived from patients with a stem cell disease

Grant Award Details

Self-renewal and senescence in iPS cells derived from patients with a stem cell disease

Grant Type: Basic Biology II

Grant Number: RB2-01497

Project Objective: The goal of this project is to derive and then use iPSC from patients with Dyskeratosis congenita to better understand the disease, in particular to understand the mechanisms by which various mutations in genes encoding components of the telomerase pathway cause disease.

Investigator:

Name:	Steven Artandi
Institution:	Stanford University
Type:	PI

Disease Focus: Blood Disorders, Pediatrics

Human Stem Cell Use: Embryonic Stem Cell, iPS Cell

Cell Line Generation: iPS Cell

Award Value: $931,285

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: Year 4 (NCE)

View Report

Grant Application Details

Application Title: Self-renewal and senescence in iPS cells derived from patients with a stem cell disease

Public Abstract:

The discovery of induced pluripotent stem (iPS) cell technology promises to revolutionize our understanding of human disease and to allow the development of new cellular therapies for regenerative medicine applications. The ability to reprogram a patient's fibroblasts to iPS cells creates the opportunity to expand human cells with a specific genetic defect and to study that defect in a defined cell population, either to understand the basic biology of the disease or to study potential therapeutics. Furthermore, the genetic defects in iPS cells can be repaired and the iPS cells used as a source for cellular therapies after differentiation to specific cell lineages. Although tremendous strides have been made in recent years in treating human disease, replacing damaged tissue remains almost completely beyond our grasp. Harnessing human iPS stem cells for this purpose will open completely new areas of regenerative medicine. However, a limited understanding of iPS cell self-renewal and differentiation is a major roadblock in realizing this long-term goal.

One shared characteristic of iPS cells and adult stem cells that reside in many of our tissues is the ability to self-renew. Self-renewal is the ability of a stem cell to divide and give rise to a daughter cell that is undifferentiated and capable of giving rise to all the same lineages as the parent stem cell. Senescence pathways – pathways that cause dividing cells to permanently stop dividing – represents a significant barrier in the reprogramming process to engineer new iPS cells. Understanding how iPS cells self-renew is critical for determining how to maintain these cells, how to differentiate them toward specific tissue lineages and how to expand more committed stem cells or progenitor cells in cell culture.

In this proposal, we investigate the molecular mechanism of self-renewal and senescence in human iPS cells using skin cells isolated from patients with a defect in the enzyme telomerase. Telomerase is an enzyme complex expressed in embryonic stem cells, some tissue stem cells and in almost all human cancers. Most differentiated cells lack telomerase expression. Telomerase adds DNA repeats to structures at the ends of our chromosomes, termed telomeres. Telomeres are very important in protecting chromosome ends and in preventing chromosome ends from breaking down or sticking to other ends inappropriately. By maintaining telomeres, telomerase supports the ability of stem cells to divide a large number of times. People with telomerase mutations develop a stem cell disease – dykeratosis congenita. In this disease, patients have defects in skin, blood and lung – tissues that depend on tissue stem cell function to maintain these organs during life. We will reprogram skin cells from dyskeratosis patients to understand how senescence responses limit iPS cell self-renewal and differentiation to specific cell lineages.

Statement of Benefit to California:

This proposal will benefit California and its citizen in two general ways. First, I have recruited new scientists to California from Texas and from Brazil to work on this proposal. These are new taxpayers and consumers, which will benefit local businesses. They would have been less likely to come to California in the absence of the CIRM program and its strong emphasis on human stem cell biology. Second, this novel grant will generate new intellectual property in the form of patents. These patents may in fact be licensed to California companies or be used to support the formation of new start-up companies. The growth of such companies has historically fueled much of the profound growth in California. The future of California is linked to new technologies in the stem cell, biotechnology and other technology.

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